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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 211, 226, 510, and 514

[Docket No. 88N–0038]

RIN 0910–AC42

Records and Reports Concerning Experience With Approved New Animal Drugs

AGENCY: Food and Drug Administration, HHS.

ACTION: Withdrawal of interim final rule and issuance of final rule.

SUMMARY: The Food and Drug Administration (FDA) is withdrawing the interim final rule that it published on February 4, 2002. The interim final rule amended the regulations for records and reports concerning experiences with approved new animal drugs. FDA invited interested parties to comment on the interim final rule. As a result of those comments, this final rule more clearly defines the kinds of information to be maintained and submitted by new animal drug applicants for new animal drug applications (NADAs) or abbreviated new animal drug applications (ANADAs). In addition, the final rule revises the timing and content of certain reports to enhance their usefulness. This regulation will provide for protection of public and animal health and reduce unnecessary recordkeeping and reporting requirements.

DATES: This rule is effective [*insert date 90 days after date of publication in the* **Federal Register**]. The interim final rule that published at February 4, 2002 (67 FR 5046), is withdrawn as of [*insert date of publication in the* **Federal Register**].

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SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of December 17, 1991 (56 FR 65581), FDA published a proposed rule (the proposed rule for records and reports) to revise § 510.300 (21 CFR 510.300) and to redesignate it as § 514.80 (21 CFR 514.80). This regulation implements section 512(l) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360b(l)) which provides that, following approval of an NADA or ANADA, applicants must establish and maintain records and make reports to the agency as prescribed by regulation or order. We (FDA) proposed the revision in order to more clearly define the kinds of information to be maintained and submitted by the applicant and to revise the timing and content of certain reports to enhance the usefulness of the information.

After considering comments submitted in response to the proposed rule for records and reports, FDA adopted the rule in modified form in an interim final rule. The scope and coverage of the interim final rule differed in some respects from the proposed rule for records and reports. The proposed rule for records and reports covered NADAs, ANADAs, and medicated feed applications (MFAs). In contrast, the interim final rule covered only NADAs

and ANADAs. The Animal Drug Availability Act of 1996 (ADAA) (21 U.S.C. 360b(a) and (m)) amended the statutory provisions in the act regarding medicated feeds and eliminated MFAs. Therefore, the interim final rule did not address MFAs. However, the interim final rule retained reporting requirements for adverse drug experiences (ADEs) with feeds incorporating approved Type A medicated articles.

While the proposed rule for records and reports proposed to remove 21 CFR 510.310, which addressed records and reports for new animal drugs approved before June 20, 1963, we issued a final rule that revoked this provision in response to the Administration's "Reinventing Government Initiative" (61 FR 37680, July 19, 1996). The proposed rule for records and reports followed a style and format similar to the human drug records and reports regulations in part 314 (21 CFR part 314). The interim final rule maintained a similar style and format, but removed many of the proposed records and reports requirements that are not necessary to monitor animal drugs.

In response to initial concerns over duplicate reporting, FDA had removed proposed § 514.82 from the interim final rule, which concerned records and reports from manufacturers, packers, labelers, and distributors other than the applicant. However, the agency did retain certain record and report requirements for nonapplicants (defined in new § 514.3) (21 CFR 514.3)) and in § 514.80(b) of the interim final rule. Under § 514.80(b)(3), nonapplicants must submit reports of adverse events to applicants and, if they choose, also to FDA. FDA requires such reports under the authority of sections 501 and 701 of the act (21 U.S.C. 351 and 371) and section 512(l) of the act. Keeping track of such reports helps the agency assure that the new animal drug meets

the requirements of the act as to safety as required by section 501. Additionally, section 512(l) requires applicants to report adverse events that the applicant has "received or otherwise obtained." In this instance, FDA is requiring that the applicant "receive" reports from other parties that are listed on the label by requiring that the nonapplicants give the reports to the applicants. For purposes of clarity, the agency also made some changes to the text and organization of the interim final rule.

On February 4, 2002, the interim final rule on ADE records and reports was published in the **Federal Register** with an effective date of August 5, 2002 (67 FR 5046). In the **Federal Register** of July 31, 2002 (67 FR 49568), the effective date of the interim final rule published at 67 FR 5046 was delayed indefinitely. We received and reviewed 33 comments on the interim final rule from 4 commenters. In response to those comments, we are withdrawing the interim final rule that published on February 4, 2002 (67 FR 5046), and issuing this final rule.

II. Comments on the Interim Final Rule

The agency received four sets of comments on the interim final rule for records and reports, three from industry associations, and one from a pharmaceutical company. A discussion of the comments and our response follows. In the interest of clarity, the comments are addressed by relevant section of the rule, with general comments following.

A. Definition of Adverse Drug Experience (§ 514.3)

(Comment 1) One comment suggested that the definition of "Adverse Drug Experience" be changed from "Failure of a new animal drug to produce its expected pharmacological or clinical effect (lack of effectiveness)" to "Unusual

failure of a new animal drug to produce its expected pharmacological or clinical effect (lack of effectiveness)." The comment states that it is the unusual failure to respond to therapy that is of concern. The agency stated in comment 7 of the preamble to the interim final rule that failures to respond to therapy were expected. The comment responded "that current product labeling does not usually address efficacy failures." According to the comment, a failure not listed on the label would be considered unexpected and thus must be a 15-day NADA/ANADA alert report.

FDA agrees with the comment and does not intend for all effectiveness failures to be defined as ADEs. To this end, FDA will clarify the definition by changing the phrase "expected pharmacological or clinical effect (lack of effectiveness)" to "expected pharmacological or clinical effect (lack of expected effectiveness)." FDA also will continue to work with applicants and provide advice to applicants in determining reportable events. For example, consider a drug that is expected to cure 80 percent of the animals treated, but cures 90 percent. While there is still a 10 percent failure rate, the success rate is above the expected rate of 80 percent; therefore, this is not a reportable ADE. However, if a drug is expected to cure 80 percent of the animals treated, but cures only 40 percent, which is a 60 percent failure rate and below the expected rate, a reportable ADE has occurred. This would be reported as a 15-day NADA/ANADA alert report since it is an unexpected ADE.

B. Definition of Applicant (§ 514.3)

(Comment 2) One comment suggested that the definition of "Applicant" be changed from "Applicant is a person who owns a new animal drug application or ANADA" to "Applicant is a person who holds a new animal drug application or an ANADA." The comment explained that the actual

owner of an application may be different from the sponsor of the application. It may be a parent company with the U.S. company being the sponsor. The comment agreed with the agency's statement in the preamble to the interim final rule that the term "applicant is limited to the holder of an approved application (NADA or ANADA) * * *."

The agency will revise the definition of "applicant" in § 514.3 as follows:

"*Applicant* is a person or entity who owns or holds on behalf of the owner the approval for an NADA or an ANADA, and is responsible for compliance with applicable provisions of the act and regulations."

C. Definition of Increased Frequency of Adverse Drug Experience and Summary Report of Increased Frequency of Adverse Drug Experience (§§ 514.3 and 514.80(b)(2)(iii))

(Comment 3) One comment requested that FDA provide additional clarification of this requirement or delete the requirement of a summary report. The comment acknowledged and appreciated FDA's willingness to make changes in response to previous comments. However, it stated that there are doubts that this requirement can be met "even with the adjustment for drug exposure." The comment stated that the adjustment for drug exposure based on distribution data would be unreliable given that distribution data does not "equate[d] with the amount actually used (exposure) in any given time period." Also, the comment maintained that this requirement of a summary report is "troubling" because it is required to be submitted within 15 working days.

In retrospect, FDA does concur with the concern about requiring summary reports within 15 working days. FDA has modified § 514.80(b)(2)(iii) to require that information be reported in the 6-month and yearly periodic drug

experience reports under § 514.80(b)(4)(v). FDA also has made a conforming change to § 514.80(a)(4) to include § 514.80(b)(4)(v).

The following is the change to former § 514.80(b)(2)(iii), now under § 514.80(b)(4)(v):

(v) *Summary report of increased frequency of adverse drug experience.* The applicant must periodically review the incidence of reports of adverse drug experiences to determine if there has been an increased frequency of serious (expected and unexpected) adverse drug events. The applicant must evaluate the increased frequency of serious (expected or unexpected) adverse drug events at least as often as reporting of periodic drug experience reports. The applicant must report the increased frequency of serious (expected and unexpected) adverse drug events in the periodic drug experience report. Summaries of reports of increased frequency of adverse drug events must be submitted in narrative form. The summaries must state the time period on which the increased frequency is based, time period comparisons in determining increased frequency, references to any previously submitted Form FDA 1932, the method of analysis, and the interpretation of the results. The summaries must be submitted in a separate section within the periodic drug experience report.

The following is the change to § 514.80(a)(4):

"(4) The requirements of this section also apply to any approved Type A medicated article. In addition, the requirements contained in § 514.80(b)(1), (b)(2), (b)(4)(iv), and (b)(4)(v) apply to any approved Type A medicated article incorporated in animal feeds."

D. Definition of Serious Adverse Drug Experience (§ 514.3)

(Comment 4) One comment asked FDA to change the definition of a "Serious adverse drug experience" from "an adverse event that is fatal or life threatening, requires professional intervention." to "an adverse event that is

fatal or is a life-threatening event that requires professional intervention.'' The comment stated that the listing of events ''adds confusion as to whether all or just one of the conditions need to be present for the event to meet the definition of serious.'' The comment questioned whether ''professional intervention'' is necessary for every listed condition in the definition for the event to be considered a serious ADE. Another comment asked that ''requires professional intervention'' be removed from the list since some events involving veterinary intervention are not serious.

In order to clarify the issue, FDA has added ''or'' between each term so that it is clear that each event listed is independent of any other event. Any one of the events listed will be considered a serious ADE. Both comments suggest that the ADE be considered serious only in the case where the fatal or life-threatening event requires professional intervention. FDA believes that a fatal or life-threatening event is serious regardless of whether professional intervention is sought for treatment. Thus, FDA will not change the definition to require professional intervention for each event. Events that are life threatening or that require professional intervention will be considered serious ADEs. FDA believes that any professional veterinary intervention is serious enough in nature to require reporting.

(Comment 5) One comment requested clarification of the portion of the definition that ''requires professional intervention'' as to whether this means that any reports from veterinarians to the applicant are considered serious.

FDA addressed this issue in comment 10 of the preamble in the interim final rule and added professional intervention to clarify the definition of seriousness for animal drugs. We believe that the definition is appropriate.

(Comment 6) One comment questioned whether "infertility" is a serious ADE. The comment stated that infertility following administration is rarely drug-related, and that many types of infertility would not be serious.

We disagree with the comment. Purebred producers (e.g., of cats, dogs, or cattle) would not want to use a product that may impair fertility unless necessary. Therefore, FDA believes that it is important to make label changes regarding fertility as quickly as possible, thus providing important labeling information for the end user. FDA will not remove "infertility" from the definition.

(Comment 7) One comment stated that the "unique aspects of evaluating animals that are housed and managed as a group" should be included in the definition. The comment proposed that FDA use the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) definition of serious ADE. The comment used an example situation in which the background frequency of death in animals not treated is higher than animals treated with the drug. FDA addressed a similar issue in the preamble of the interim final rule under comment 7. The VICH guidance documents are in early development, and once completed it is the intention of FDA to adopt and implement them in a manner consistent with its existing regulations. At this time, it is premature to adopt VICH definitions.

(Comment 8) One comment stated that a patient examination should not be considered professional intervention if there is no administration or dispensing of medications. According to the comment, this should not be the sole means of classifying an event as serious. The comment further stated that if there is an examination and no treatment is indicated by the veterinarian, then "professional intervention in the outcome of the case has not occurred."

An examination with no medical or surgical intervention/treatment or any treatment is a reportable ADE. If professional services of a veterinarian are engaged then this is considered an intervention incident. For example, if an over-the-counter (OTC) or prescription (Rx) drug product is given to the animal prior to veterinary intervention and an adverse drug reaction occurs, then the veterinarian, upon examination, may have important information concerning the event. As explained in the preamble of the interim final rule, FDA added the words "professional intervention" to clarify the definition of seriousness for animal drugs. FDA believes that the definition is appropriate.

The following is the change to the definition for "serious adverse drug experience" in § 514.3:

"*Serious adverse drug experience* is an adverse event that is fatal, or life-threatening, or requires professional intervention, or causes an abortion, or stillbirth, or infertility, or congenital anomaly, or prolonged or permanent disability, or disfigurement."

E. Definition of Unexpected Adverse Drug Experience (§ 514.3)

(Comment 9) One comment suggested that FDA change the definition of "Unexpected drug experience" from "an adverse event that is not listed in the current labeling for the new animal drug." to "an adverse event that is not listed in the current labeling for the new animal drug or reported in its Freedom of Information Summary(ies)." The comment highlighted the inclusion of the NADA file in the current rule's definition of "unexpected drug experience" and that those incidences referenced in the NADA file may not be captured on the label. Therefore, there is concern that this change from the current § 510.300(b)(2)(i) will increase the number of reports to the NADA file. There is also a concern that this would increase FDA's workload for labeling

changes, especially for Type A medicated articles and OTC products. The comment maintained that it is inappropriate for FDA to exclude the NADA file, and include only the current label, from the definition since the freedom of information summary of the NADA file is publicly available. The comment further stated that it is inappropriate since the applicant is the primary source of the ADE and is responsible for determining if the report is unexpected.

We disagree with the comment. Although the freedom of information summary is a publicly available document, it is neither a practical substitute for a label, nor is it widely distributed and available with the label.

(Comment 10) One comment posed a scenario where an ADE is commonly recognized and not on the current label. It suggested that since the ADE is commonly recognized, it should be expected by FDA. The comment asked for the agency's expectation/position on this scenario.

FDA requires that recognized ADEs be on the label. It is the position of the Center for Veterinary Medicine (CVM) that any serious, unexpected ADE be reported under § 514.80(b)(2).

F. Applicability of Records and Reports Concerning Experience With Approved New Animal Drugs (§ 514.80(a)(1))

(Comment 11) One comment objected to the requirement of "separate" filing systems in the sentence "Each applicant and nonapplicant must establish and maintain indexed, separate, and * * *" The comment stated that this is a new requirement not present in the proposed rule for records and reports and it is not in § 514.300(a). Further, the comment argued that it is the applicant's decision to determine whether files are stored separately or as part of another filing system. The comment requested an explanation for this change, and proposed that the word "separate" be deleted.

It was not FDA's intention to make the determination as to whether files are stored separately or as part of another filing system. During FDA's review of comments on the proposed rule for records and reports concerning duplicate reporting, it was determined that the proposed § 514.82 (nonapplicant) information should be combined with proposed § 514.80 (applicant) information. The use of the word "separate" in this sentence was FDA's attempt to combine the information from proposed § 514.82 with § 514.80. Unfortunately, the combined verbiage has lead to this unintended reading by the commenter. Also, it was not FDA's intention that nonapplicants "establish and maintain indexed, separate, and complete files containing full records of all information * * * of a new animal drug * * *" It is the intention of FDA that nonapplicants "establish and maintain indexed, separate, and * * *" of only the information that they receive or otherwise obtain. Therefore, FDA has separated requirements for applicants from requirements for nonapplicants in order to clarify the meaning.

(Comment 12) One comment proposed that the clause "* * * that has not been previously submitted as part of the NADA or ANADA" be changed to "* * * that has not been previously submitted as part of an investigational new animal drug (INAD) file, the NADA or ANADA." The comment expressed concern that the studies/information submitted to the INAD would be excluded from the exemption of being "previously submitted" until the sponsor incorporated the information by reference into the NADA/ANADA file.

FDA believes that changing the regulation to include INADs is outside the scope of this regulation. The scope of records and reports is for experiences with approved new animal drugs, not investigational uses. The consequences of adding INADs to this regulation would be that applicants of INADs would

have to submit the information and data under § 514.80. Therefore, FDA will not change the regulation to include INADs.

The following is the change to (§ 514.80(a)(1)):

(a) *Applicability.* (1) Each applicant must establish and maintain indexed and complete files containing full records of all information pertinent to safety or effectiveness of a new animal drug that has not been previously submitted as part of the NADA or ANADA. Such records must include information from domestic as well as foreign sources.

Each nonapplicant must establish and maintain indexed and complete files containing full records of all information pertinent to safety or effectiveness of a new animal drug that is received or otherwise obtained by the nonapplicant. Such records must include information from domestic as well as foreign sources.

G. Three-Day NADA/ANADA Field Alert Report (§ 514.80(b)(1))

(Comment 13) One comment asked what district office should be notified for 3-day NADA/ANADA field alert reports for U.S.-approved products that are manufactured outside of the United States.

Applicants should contact their FDA district office to determine the procedure for reporting 3-day alerts.

H. Fifteen-Day NADA/ANADA Alert Report (§ 514.80(b)(2))

(Comment 14) One comment opposed the use of the terminology "regardless of source of the information" in the reporting requirement for 15-day NADA/ANADA alert reports. The comment stated that "regardless of source" is overly broad. According to the comment, an ADE found by an employee of the company while browsing a chat room on the Internet would have to be reported to FDA. The comment also expressed concern that serious adverse events outside the United States be reported to FDA within 15 days.

The phrase "regardless of source" was added to emphasize that the agency wanted all reports of ADEs. A legitimate source is an identifiable reporter, an identifiable product, and one or more ADEs in animals or humans, regardless of whether the source is the Internet. If the event is a serious, unexpected adverse drug event then it must be reported in a 15-day NADA/ANADA alert report. All domestic and foreign ADEs for the U.S.-approved application should be submitted under § 514.80(b)(2) or (b)(4)(iv).

(Comment 15) One comment requested that FDA elaborate on the requirement of submission of reports of ADEs from foreign sources as it relates to § 514.80(a)(2). The comment stated that this requirement is not consistent with § 510.300 and will increase the number of reports.

The burden for reporting domestic and foreign ADEs is the same under § 510.300. Foreign ADEs are required to be reported under the current regulations, although this requirement is not stated as explicitly in the current regulation as under § 514.80(a)(2). FDA is adding the language concerning foreign sources in order to make the rule more clear.

(Comment 16) One comment requested that applicants should not have to report cases where the reporter believes that an event is not drug related and the reporter does not want the case to be filed with FDA.

The ADE must be reported regardless of whether or not the reporter considers it to be drug related, if it meets the definition of an ADE (see 21 CFR 514.3), or whether a caller wishes it not to be reported. FDA will provide assistance on a case-by-case basis for specific incidences that the applicant or other reporter still believes should be excluded.

I. Nonapplicant Report (§ 514.80(b)(3))

(Comment 17) One comment recommended that in order to avoid confusion and over-reporting, all ADE reports should be submitted to CVM by the applicant, and that the sentence "if the nonapplicant elects to also report directly to FDA, the nonapplicant should submit the report on Form FDA 1932 within 15 working days of first receiving the information" should be deleted from the regulation. The comment maintained that if the nonapplicant reports to FDA in the 15-day period and it is determined by the applicant that it is not a serious, unexpected event, FDA might come to the conclusion that the applicant is under-reporting.

FDA does not concur with this recommendation. FDA believes that it is important for the nonapplicant to have a mechanism to report voluntarily. FDA will evaluate any nonapplicant report it receives to determine whether the report is of a serious, unexpected ADE.

J. Periodic Drug Experience Report—Distribution Data (§ 514.80(b)(4)(i))

(Comment 18) One comment questioned the need to report distribution data on the amounts of product exported outside the United States, and if the data are to be reported, how they will be used. The comment stated that since foreign ADEs are not required to be reported, there is no benefit for reporting amounts exported.

Foreign reports have to be submitted under § 514.80. Foreign ADEs for the U.S.-approved application must be submitted under § 514.80(b)(2) or (b)(4)(iv). These data will be used in a similar manner as domestic distribution data in determining if an increased frequency of ADE exists.

K. Periodic Drug Experience Report—Nonclinical Laboratory Studies and Clinical Data Not Previously Reported (§ 514.80(b)(4)(iii))

(Comment 19) One comment maintained that studies conducted to support a future claim should not be reported in the periodic drug experience report. The comment suggested that because sponsors make submissions to CVM's Office of New Animal Drug Evaluation (ONADE) for its review, and also report to CVM's Office of Surveillance and Compliance, the confusion could be eliminated by changing the title of this section from "Nonclinical laboratory studies and clinical data not previously reported" to "Nonclinical laboratory studies and clinical data not previously submitted."

FDA believes that such a change is not necessary. This requirement only pertains to data not previously reported to CVM, including submissions to ONADE and reports to the Office of Surveillance and Compliance.

L. Periodic Drug Experience Report—Nonclinical Laboratory Studies and Clinical Data Not Previously Reported—Prepublication Manuscripts (§ 514.80(b)(4)(iii)(C))

(Comment 20) One comment questioned the value and need to submit prepublication manuscripts and strongly recommended deletion of this requirement. The comment stated that such manuscripts are no better than draft reports and submission of these to entities other than the publisher may be prohibited by a journal in its publication policy. Additionally, it stated that the applicant could comply with the requirements for submission of a study within 1 year of its completion only when the study is conducted by or for the applicant.

FDA concurs with the recommendation and has revised this section of the regulation.

The following is the change to § 514.80(b)(4)(iii)(C):

(C) Descriptions of completed clinical trials conducted by or for the applicant must be submitted no later than 1 year after completion of research. Supporting information is not to be reported.

M. Periodic Drug Experience Report—Adverse Drug Experiences (§ 514.80(b)(4)(iv))

(Comment 21) One comment stated that FDA limited the scope of a manufacturing/product defect by changing the definition in § 514.80(g) in response to comment 12 of the interim final rule. The comment stated, "the scope of what is considered to be a manufacturing/product defect has now been limited to that which is a problem associated with public health or animal safety or that is a significant, chemical, physical, or other change or deterioration in the drug product or significant defective packaging or labeling error." According to the comment, nonsignificant defects, which involve the physical appearance but have no impact on animal safety or public health, do not need to be reported since these defects are not included in the definition of manufacturing/product defects. The comment provided a specific example of a blister unit with a misaligned die-cut of a blister, which does not affect the integrity of the package seal or labeling or an empty blister well.

Manufacturing/product defects are defined in § 514.3. If a problem with the product does not fall under the definition in § 514.3, then it is not considered a manufacturing/product defect. The example of a misaligned die-cut of a blister unit may or may not be considered a manufacturer/product defect depending on whether it is or is not a deviation of a distributed product from the standard specified in the approved application or any other portion of the definition. Manufacturing/product defects that may result in a serious

adverse drug event must be submitted as a 3-day NADA/ANADA field alert report. The requirement of a serious adverse drug event limits the number of 3-day reports. Nonserious manufacturing/product defects should be submitted in the periodic drug experience report. The manufacturing/product defects definition given in § 514.3 does not pertain to the good manufacturing practice (GMP) regulations or other regulations outside of § 514.80.

N. Periodic Drug Experience Report—Adverse Drug Experiences Not Previously Reported (§ 514.80(b)(4)(iv)(A))

(Comment 22) One comment suggested that product/manufacturing defects, other than serious ones, should not have to be reported. FDA stated in the preamble of the interim final rule that FDA would limit its scope to problems associated with public health or animal safety. According to the comment, the requirement of reporting product/manufacturing defects, other than serious ones, is not consistent with FDA's statement. The comment requested that 21 CFR 514.80(b)(4)(iv)(A) refer only to ADEs.

FDA declines to make the proposed change because eliminating the provision as requested would leave a significant gap in the safety and effectiveness profile of a drug product. The agency would no longer receive information for product and manufacturing defects that may result in "nonserious" but significant unexpected adverse drug events, i.e., events not listed on the label of a particular drug product. These could include new symptoms and pathophysiologically-related events such as increases in enzymes or blood counts that appear not to be serious by definition, but could negatively impact the effect of the drug product. Further, the applicant would not have to report product and manufacturing defects that may result in a lack of expected effectiveness.

O. Periodic Drug Experience Report—Adverse Drug Experiences in the Literature (§ 514.80(b)(4)(iv)(B))

(Comment 23) One comment stated that applicants routinely have not submitted ADEs separate from the literature. According to the comment, applicants have limited ability to investigate incidents such as studies conducted by unrelated third parties. The comment requested that this section be deleted or reworded to clarify FDA's intent.

FDA is not requesting that each individual ADE in the literature be submitted on Form FDA 1932. The use of Form FDA 1932 does not apply to § 514.80(b)(4)(iv)(B). As the rule states, FDA is asking that "a bibliography of pertinent references" of the literature containing ADEs be submitted. A bibliographic listing from Medline or other database searches would be acceptable.

P. Periodic Drug Experience Report—Adverse Drug Experiences Occurring in Postapproval Studies That Are Not Previously Reported (§ 514.80(b)(4)(iv)(C))

(Comment 24) One comment noted that reporting ADEs from postapproval studies is duplicate reporting given that the study report is submitted to ONADE. The comment contended that this would be a considerable additional workload, especially for the first 2 years postapproval. Also, if this reporting requirement is not changed, the comment asked if FDA wanted these reports on Form FDA 1932. FDA disagrees that this would be additional work. This requirement only pertains to ADEs not previously reported to CVM. Any study reports previously submitted to ONADE do not have to be submitted again. Applicants are not required to submit these experiences on Form FDA 1932.

Q. Other Reporting—Advertisements and Promotional Labeling (§ 514.80(b)(5)(ii))

(Comment 25) One comment stated that the regulation is not clear about the submission requirements for OTC and Rx promotional labeling. Further, the comment requested that the promotional labeling requirement be applicable to Rx products only, in accordance with current regulations.

FDA believes that the regulation is clear about the submission requirement for OTC and Rx labeling. FDA declines to change the applicability to Rx products only. This is not a new proposal; it was included in the proposed rule for records and reports.

R. Other Reporting—Distributor's Statement—Current Product Labeling (§ 514.80(b)(5)(iii)(A)(1))

(Comment 26) One comment suggested that, with regard to distributor's labeling, the qualifying phrase should not be limited to "manufactured for" or "distributed by." The comment argued that § 201.1(h)(5) (21 CFR 201.1(h)(5)) provides the appropriate alternatives, which should also be permitted, and recommended that the last sentence in this section be changed.

The agency concurs with the proposed revision and has revised this section.

The following is the change to § 514.80(b)(5)(iii)(A)(*1*):

(1) The distributor's labeling must be identical to that in the approved NADA/ANADA except for a different and suitable proprietary name (if used) and the name and address of the distributor. The name and address of the distributor must be preceded by an appropriate qualifying phrase as permitted by the regulations such as "manufactured for" or "distributed by."

S. Other Reporting—Distributor's Signed Statements (§ 514.80(b)(5)(iii)(B)(2) and (b)(5)(iii)(B)(3))

(Comment 27) One comment noted that the current regulation § 514.8(a)(6)(iii) (21 CFR 514.8(a)(6)(iii)) requires the distributor to state that he/she will distribute the drug only under its approved labeling and that any other labeling or advertising will prescribe, recommend, or suggest use only under the approved labeling. According to the comment, § 514.80(b)(5)(iii)(B)(*2*) and (b)(5)(iii)(B)(*3*) of the interim final rule omits the limitation on promotional labeling. The comment suggested that the language of 21 CFR 514.8(a)(6)(iii) be changed so that paragraph (b)(5)(iii)(B)(*3*) would read as follows: "(3) that the distributor will distribute the product only for use under the conditions stated in the approved labeling, and any other labeling or advertising will prescribe, recommend, or suggest its use only under the approved labeling."

The agency believes that the provisions of paragraph (b)(5)(iii)(B)(*3*) of the proposed rules are similar to those of § 514.8(a)(6)(iii), but have been simplified and written in plain language. However, to make the meaning clear, the agency has revised the section by replacing the word "advertise" with "promote."

The following is the change to § 514.80(b)(5)(iii)(B)(*3*):

"(3) That the distributor will promote the product only for use under the conditions stated in the approved labeling;"

T. Multiple Applications—Information Specific to a Particular NADA/ANADA (§ 514.80(c)(4))

(Comment 28) One comment stated that the requirements under "Multiple Applications" do not appear to decrease, but may increase the burden on the applicant. In particular, the comment questioned the requirement under

§ 514.80(c)(4) and requested clarification. The comment also expressed concern with the increased reporting burden due to the increasing number of approved combinations of drugs for use in feeds since the implementation of the ADAA. Further complicating the reporting issue is that frequently there are nonapplicants involved in the marketing of these combinations. The comment stated that, with the exception of "promotional literature," there is rarely any other information to be reported. The comment suggested that the "promotional literature" be submitted to the application held by either party—i.e., the nonapplicants or applicant—and not the application approved for the use of the combination of drugs.

The provision of the regulation in question is currently codified under § 510.300(b)(4)(ii). The current regulation and the proposal in the interim final rule are similar. There is no increase of the reporting burden. It is not the intention of FDA for the implementation of § 514.80(c) to be different from the current requirement under § 510.300(b)(4)(ii). Only information specific to a particular NADA/ANADA that is not common to all the applications must be included in the report for that particular NADA/ANADA, for example, labeling. With regard to the comment that there is an increased reporting burden due to the ADAA, increased reporting is due to the increased number of approved applications, and not due to different requirements. FDA consequently believes that this is a reasonable reporting requirement.

U. Records to Be Maintained and Access to Records and Reports (§ 514.80(e) and (f))

(Comment 29) One comment asked where the primary repository for foreign report records (United States versus the foreign country) would reside.

Sponsors should keep records wherever it is their customary business practice to keep them as long as the records are available to FDA for inspection.

V. General Comments on the Regulation

(Comment 30) One comment requested that CVM adopt procedures for waiving the reporting of ADEs for NADAs/ANADAs. The comment suggested adopting procedures similar to FDA's Center for Drug Evaluation and Research's March 2001 draft publication entitled "Guidance for Industry on Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines." This guidance states that applicants under certain conditions may request waivers from submission of full ADE reports that are both nonserious and labeled.

We disagree with the comment. The procedures in the draft guidance cited by the commenter only waive reporting such adverse experiences on FDA Form 3500A. The applicant still must collect and report these adverse experiences by providing a summary tabulation by body system and a narrative discussion about all adverse experiences in the periodic report. FDA also may request that the applicant submit these reports on the human form (FDA Form 3500A) within 5 calendar days after receipt of the agency's request. The final records and reports rule does not include such a summary tabulation or narrative discussion requirement. We believe that adding such a requirement would impose a greater burden on the regulated industry than the requirement of reporting such adverse events on Form FDA 1932 in periodic reports. Further, we believe it is crucial that all adverse drug experience information be submitted in a consistent manner and format to facilitate the agency's analysis of the information. For these reasons, we have not adopted the change proposed by this comment.

(Comment 31) One comment asked if ADEs and product defects for unapproved products, which meet the requirements of 21 CFR part 801(e)(1) of the act, should be reported.

No, this regulation only pertains to approved new animal drugs.

(Comment 32) One comment asked if a validated electronic signature in compliance with part 11 (21 CFR part 11) would suffice for an authorized signature on Form FDA 1932.

Yes, an electronic signature that is compliant with part 11 will be acceptable.

(Comment 33) One comment apparently has misinterpreted the table that outlines the purpose of each paragraph. In particular, the comment indicated belief that the purpose given for § 514.80(b)(1) also pertained to the next line § 514.80(b)(2).

FDA believes that the commenter has simply misinterpreted the table. Section 514.80(b)(1) and (b)(2) are separate line items in the table. The confusion appears to be because the purpose column for § 514.80(b)(2) is blank because the subsequent three titles are subsections of § 514.80(b)(2), i.e., § 514.80(b)(2)(i) through (b)(2)(iii). Thus, a blank in the purpose column does not mean the preceding description applies. For clarity's sake, however, FDA has added the phrase "See paragraphs below" in place of the blank spaces.

III. Summary of the Final Rule

FDA is affirming the interim final rule on its requirements for records and reports concerning experiences with approved new animal drugs (67 FR 5046) with modifications. The modifications include: Revising the definitions of "applicant" and "serious adverse drug experience;" modifying the reporting requirement for summary reports of increased frequency of ADEs; clarifying

what safety and efficacy records a nonapplicant versus an applicant must maintain; eliminating the requirement of submission of prepublication manuscripts relating to completed clinical trials; changing distributor's labeling so that the qualifying phrase that must precede the name and address of the distributor is as permitted by § 201.1; and revising the section of the rule pertaining to distributor's signed statements to state that the distributor will promote the product only for use under the conditions stated in the approved labeling.

IV. Conforming Changes

With the amendment of the animal drug regulations, certain revisions to parts 226, 510, and 514 (21 CFR parts 226, 510, and 514) and 21 CFR part 211 are required to conform to the designations in the amendments. Certain other provisions of part 510 and § 514.8 are superseded by these regulations and are removed.

V. Environmental Impact

FDA has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VI. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the

distribution of power and responsibilities among the various levels of government. Accordingly, the agency has concluded that the rule does not contain policies that have federalism implications as defined in the order and, consequently, a federalism summary impact statement is not required.

VII. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612) and the Unfunded Mandates Reform Act (Public Law 104–4). The Office of Management and Budget (OMB) has determined that this final rule is a significant regulatory action subject to review under Executive Order 12866. FDA also certifies in accordance with the Regulatory Flexibility Act that this rule will not have a significant economic impact on a substantial number of small entities, and therefore, a regulatory flexibility analysis is not required. Further, the Unfunded Mandates Reform Act does not require FDA to prepare a statement of costs and benefits for the final rule because it is not expected to result in any 1-year expenditure that would exceed $100 million adjusted for inflation. The current inflation-adjusted statutory threshold is about $110 million.

The regulation is intended to clarify and simplify recordkeeping requirements while improving the protection of public and animal health. The revisions in the reporting requirements are expected to provide savings through lower recordkeeping costs in some areas while imposing small cost increases due to requirements for recordkeeping of more useful information.

In the rule, the term "applicant" is limited to the holder of an approved application (NADA or ANADA) and does not include every firm whose name appears on product labeling, as the regulations previously provided. A nonapplicant is required to send copies of necessary information to the

applicant who would then combine all information received, whether from one or several sources, and submit a single report to FDA. This change would reduce paperwork requirements because firms would be required to submit fewer reports. Also, those reports should provide for a more comprehensive reporting of all required information.

The current requirement for ADE reports to be submitted by distributors is retained under the final rule in § 514.80(b)(3) in nonapplicant reporting. The requirement for any firm involved in the manufacturing, processing, packing, labeling, or distributing of a new animal drug product other than the applicant (the nonapplicant) to report adverse experiences either to FDA or to the applicant is a restatement of the previous provisions of § 510.300(f) that applies to a small number of firms that would not routinely be expected to receive such information. The restatement is intended to clearly state that any such information received is required to be reported to FDA, either directly or through the applicant. However, only one party would be required to file the report.

The revised regulations amend the language of the regulations to clarify current practices. The conformity of reporting requirements for animal drugs and human drugs may simplify the process for firms that manufacture both kinds of products. No added costs are expected for those firms that only manufacture new animal drug products. In the past, FDA has required that records and reports be retained for an indefinite period. The proposed rule provided for a retention period of 10 years. In response to industry comments, FDA changed this requirement in the interim final rule to 5 years for all information. This would provide an additional opportunity for savings compared to the proposed rule. No additional comments were received on this

issue, and the 5-year retention period has been retained in the final rule. Since the current average length of time which records are kept is unknown, it is possible that there will be a small net cost due to this provision, even though the reporting requirements are clarified for easier compliance and administration.

The previously existing regulation required reports concerning newly approved NADAs and ANADAs every 6 months for the first year and annually thereafter. The proposed rule for records and reports would have required submission of such reports at quarterly intervals for 3 years following approval. FDA agrees with comments from industry that the proposed rule's requirement of reports at quarterly intervals for 3 years following approval was unnecessary, and the agency decreased the reporting requirements in the interim final rule. No additional comments were received on this issue. The final rule requires reports of ADEs to be submitted every 6 months for 2 years and annually thereafter.

The net change from the previous regulation requires one additional report in the second year. FDA estimates that it approves 30 NADAs annually. FDA estimates that 13.6 hours are required to establish and maintain the drug experience data, as well as write the report. Total hours required for this provision are estimated at 408. At a middle manager's estimated total wage rate of about $35 per hour, this provision would cost $14,280 annually. Moreover, applicants may petition for lengthier report intervals. FDA will provide for reporting at intervals longer than 1 year when justified based on current experience or manufacturing and marketing status. The expected number of petitions for reporting at intervals greater than 1 year is difficult to estimate because it depends on the extent to which each individual

company wishes to qualify for this provision. The net result of these two provisions may be either a very small cost or savings to each firm.

The interim final rule would have required applicants to periodically review the incidence of ADEs and report any significant increase in the frequency to FDA as soon as possible or within 15 working days of determining a significant increase in frequency exists. In response to comments, the final rule provides more flexibility to industry by allowing these reports to be submitted in the periodic drug experience reports rather than within the 15-day period. FDA expects to receive very few of these reports each year and estimates that the annual number will be between 1 and 20. These reports would not be expected to take more than 1 to 2 hours of a manager's time, and the high-end estimated cost to industry would be $1,400 annually. Periodic review of ADE reports, although on a less formal basis, is currently understood to be normal business practice.

The net costs and benefits of this final rule, though indeterminate, are expected to be modest. FDA concludes that the impacts of the final rule do not qualify it as an economically significant rule as defined under Executive Order 12866.

The Regulatory Flexibility Act, as amended (5 U.S.C. 601–612), allows for a waiver of the regulatory flexibility analysis if an agency certifies there will not be a significant impact on a substantial number of small entities as a result of a rule, as well as provides the factual basis for such a certification. The Small Business Administration definition of a small business in this industry category is limited to those firms with less than 750 employees. It is expected that a substantial number of the firms that will be subject to the new recordkeeping and reporting requirements will meet the definition of small

businesses. FDA estimates that from 1 to 13 of the approximately 30 NADA and ANADA approvals in 1999 may have been from small businesses. Using the upper end of this range, about 42 percent of the firms receiving approval annually would be subject to the new recordkeeping and reporting requirements. This regulation is not expected to have a significant economic impact on these firms because the final rule is intended to simplify and clarify current recordkeeping and reporting requirements. The net costs and benefits on each small firm are expected to be modest. Accordingly, FDA certifies in accordance with the Regulatory Flexibility Act (5 U.S.C. 601–612) that this rule will not have a significant economic impact on a substantial number of small entities. A regulatory flexibility analysis, therefore, is not required.

VIII. Paperwork Reduction Act of 1995

This final rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501–3520). A description of these provisions is given below. Included is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

Title: Records and Reports Concerning Experience With Approved New Animal Drugs.

Description: This final rule amends the provisions of the animal drug regulations concerning requirements for recordkeeping and reports concerning experience with approved new animal drugs. The information contained in the reports required by this rule enables FDA to monitor the use of new animal drugs after approval and to ensure their continued safety and efficacy. The reporting requirements include: A report that provides information on product

and manufacturing defects that may result in serious adverse drug events within 3 days of becoming aware the defect exists (new § 514.80(b)(1)); a report that provides information on serious and unexpected adverse drug events and a followup report on such events (new § 514.80(b)(2)); a summary report of increased frequency of ADEs (new § 514.80(b)(4)(v)); a report from nonapplicants, such as distributors, to applicants providing information on ADEs (new § 514.80(b)(3)); a periodic report with information on distribution, labeling, manufacturing or controls changes, new laboratory studies, and all adverse events in the reporting period (new § 514.80(b)(4)); and other reports that include special drug experience reports; reports for advertising and promotional labeling, and reports for distributor statements (new § 514.80(b)(5)). These reports must be kept for 5 years (new § 514.80(e)).

The final rule strengthens the current reporting system by requiring periodic reports every 6 months for the first 2 years following initial approval of an application rather than just for the first year following initial approval. The increased burden on applicants amounts to one additional periodic report. While greater than the reporting burden in the previous rule, this burden is less than that of the proposed rule which would have required quarterly periodic reports for 3 years following initial approval.

All periodic reports must be submitted with Form FDA 2301, "Transmittal of Periodic Reports and Promotional Materials for New Animal Drugs" (OMB control number 0910–0012). ADE reports must be submitted on Form FDA 1932, "Veterinary Adverse Drug Reaction, Lack of Effectiveness, Product Defect Report" (OMB control number 0910–0012).

In the **Federal Register** of February 4, 2002, FDA invited comments on the interim final rule and the information collection requirements. Only one

comment received pertained to information collection. That comment stated that the requirements under "Multiple Applications" do not appear to decrease but may increase the burden on the applicant. In particular, the comment questioned the requirement under § 514.80(c)(4) and requested clarification. The comment also voiced concern about an increased reporting burden due to the increasing number of approved applications for combinations of drugs for use in feeds since the implementation of the ADAA. Further complicating the reporting issue is that frequently there are nonapplicants involved in the marketing of these combinations. The comment stated that with the exception of "promotion literature," there is rarely any other information to be reported, suggesting that the "promotion literature" be submitted to the application held by either party, i.e., the nonapplicants or applicant, and not the application approved for the use of the combination of drugs.

In response, FDA notes that the provision of the regulation in question is currently codified under § 510.300(b)(4)(ii). The current regulation and the proposal in the interim final rule are similar. There is no increase of the reporting burden. It is not the intention of FDA for the implementation of § 514.80(c) to be different than the current requirement under § 510.300(b)(4)(ii). Only information specific to a particular NADA/ANADA that is not common to all the applications must be included in the report for that particular NADA/ANADA, for example, labeling. With regard to the comment that there is an increased reporting burden due to the ADAA, increased reporting is due to the increased number of approved applications, and not due to different requirements. FDA consequently believes that this is a reasonable reporting requirement.

Description of Respondents: Applicant respondents are sponsors of approved NADAs and ANADAs. Nonapplicant respondents are those, other than the applicant, involved in manufacturing, processing, packing, labeling, or distributing new animal drugs.

RECORDS AND REPORTS CONCERNING EXPERIENCE WITH APPROVED NEW ANIMAL DRUGS

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN[1]

21 CFR Section/Title/FDA Form No.	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
514 80(b)(2)(i)/Original 15-Day Alert Report/Form FDA 1932	190	55.26	12,283	1	12,283
514.80(b)(1)/3-Day Field Alert Report/ Form FDA 1932	190	0.32	95	1	95
514 80(b)(2)(ii)/Followup 15-Day Alert Report/Form FDA 1932	190	17.90	6,007	1	6,007
514.80(b)(3)/Nonapplicant Report/ Form FDA 1932	340	2.94	1,000	1	1,000
514.80(b)(4)/Periodic Drug Experience Report/Form FDA 2301, and 514.80(c) Multiple Applications[2]	190	7.11	1,226	11	13,486
514.80(b)(4)(v)/Summary Report of Increased Frequency of Adverse Drug Experience	190	1.58	300	2	600
514.80(b)(5)(i)/Special Drug Experience Report/ Form FDA 2301	190	0 13	25	2	50
514.80(b)(5)(ii)/Advertising and Promotional Materials Report/ Form FDA 2301	190	2.11	772	2	1,544
514.80(b)(5)(iii)/Distributor's Statement Report/ Form FDA 2301	530	0.14	56	2	112
Total					35,177

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.
[2] The reporting burden for § 514.80(b)(4)(iv)(A) is included in the reporting burden for § 514 80(b)(2)(i).

TABLE 2.—ESTIMATED ANNUAL RECORDKEEPING BURDEN[1]

21 CFR Section	No. of Respondents	Annual Frequency of Response	Total Annual Responses	Hours per Response	Total Hours
514 80(e)[2]	530	28.22	19,385	0.5	9,693
514.80(e)[3]	530	4.06	2,379	10.35	24,623
Total					34,316

[1] Burden estimates were separated between Form FDA 1932 and Form FDA 2301 to reflect the difference in estimates for "Hours per Respondent" required.
[2] Recordkeeping estimates for § 514.80(b)(1), (b)(2)(i), (b)(2)(ii), and (b)(3); Form FDA 1932.
[3] Recordkeeping estimates for § 514.80(b)(2)(iii), (b)(4), (b)(5), and (c); Form FDA 2301

Forms FDA 1932 and FDA 2301 for this collection of information are currently approved under OMB control number 0910–0012 and will not change due to implementation of this regulation. The reporting and recordkeeping burden estimates in this document are based on the submission of reports to the Division of Surveillance, CVM. The total annual response numbers are based on the 2000 fiscal year submission of reports to the Division of Surveillance, CVM. The numbers in tables 1 and 2 of this document are total

burden associated with this regulation. Section 514.80(b)(3) and (b)(4)(v) are new information collection requirements over the current requirements.

The information collection provisions of this final rule have been submitted to OMB for review. FDA will publish a notice in the **Federal Register** announcing OMB's decision to approve, modify, or disapprove the information collection provisions in this final rule. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

List of Subjects

21 CFR Part 211

Drugs, Labeling, Laboratories, Packaging and containers, Prescription drugs, Reporting and recordkeeping requirements, Warehouses.

21 CFR Part 226

Animal drugs, Animal feeds, Labeling, Packaging and containers, Reporting and recordkeeping requirements.

21 CFR Part 510

Administrative practice and procedure, Animal drugs, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 514

Administrative practice and procedure, Animal drugs, Confidential business information, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 211, 226, 510, and 514 are amended as follows:

PART 211—CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS

1. The authority citation for 21 CFR part 211 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 360b, 371, 374.

§ 211.198 [Amended]

2. Section 211.198 *Complaint files* is amended in paragraph (a) in the last sentence by removing "in accordance with § 310.305 of this chapter" and adding in its place "in accordance with §§ 310.305 and 514.80 of this chapter."

PART 226—CURRENT GOOD MANUFACTURING PRACTICE FOR TYPE A MEDICATED ARTICLES

3. The authority citation for 21 CFR part 226 continues to read as follows:

Authority: 21 U.S.C. 351, 352, 360b, 371, 374.

4. Section 226.1 is amended by redesignating the existing text as paragraph (a) and by adding paragraph (b) to read as follows:

§ 226.1 Current good manufacturing practice.

* * * * *

(b) In addition to maintaining records and reports required in this part, Type A medicated articles requiring approved NADAs are subject to the requirements of § 514.80 of this chapter.

PART 510—NEW ANIMAL DRUGS

5. The authority citation for 21 CFR part 510 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 360b, 371, 379e.

§ 510.300 [Removed]

6. Section 510.300 *Records and reports concerning experience with new animal drugs for which an approved application is in effect* is removed.

§ 510.302 [Removed]

7. Section 510.302 *Reporting forms* is removed.

PART 514—NEW ANIMAL DRUG APPLICATIONS

8. The authority citation for 21 CFR part 514 is revised to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 360b, 371, 379e, 381.

9. Section 514.3 is added to read as follows:

§ 514.3 Definitions.

The definition and interpretation of terms contained in this section apply to those terms as used throughout subchapter E.

Adverse drug experience is any adverse event associated with the use of a new animal drug, whether or not considered to be drug related, and whether or not the new animal drug was used in accordance with the approved labeling (i.e., used according to label directions or used in an extralabel manner, including but not limited to different route of administration, different species, different indications, or other than labeled dosage). Adverse drug experience includes, but is not limited to:

(1) An adverse event occurring in animals in the course of the use of an animal drug product by a veterinarian or by a livestock producer or other animal owner or caretaker.

(2) Failure of a new animal drug to produce its expected pharmacological or clinical effect (lack of expected effectiveness).

(3) An adverse event occurring in humans from exposure during manufacture, testing, handling, or use of a new animal drug.

ANADA is an abbreviated new animal drug application including all amendments and supplements.

Applicant is a person or entity who owns or holds on behalf of the owner the approval for an NADA or an ANADA, and is responsible for compliance with applicable provisions of the act and regulations.

Increased frequency of adverse drug experience is an increased rate of occurrence of a particular serious adverse drug event, expected or unexpected, after appropriate adjustment for drug exposure.

NADA is a new animal drug application including all amendments and supplements.

Nonapplicant is any person other than the applicant whose name appears on the label and who is engaged in manufacturing, packing, distribution, or labeling of the product.

Product defect/manufacturing defect is the deviation of a distributed product from the standards specified in the approved application, or any significant chemical, physical, or other change, or deterioration in the distributed drug product, including any microbial or chemical contamination. A manufacturing defect is a product defect caused or aggravated by a manufacturing or related process. A manufacturing defect may occur from a single event or from deficiencies inherent to the manufacturing process. These defects are generally associated with product contamination, product deterioration, manufacturing error, defective packaging, damage from disaster, or labeling error. For example, a labeling error may include any incident that causes a distributed product to be mistaken for, or its labeling applied to, another product.

Serious adverse drug experience is an adverse event that is fatal, or life-threatening, or requires professional intervention, or causes an abortion, or stillbirth, or infertility, or congenital anomaly, or prolonged or permanent disability, or disfigurement.

Unexpected adverse drug experience is an adverse event that is not listed in the current labeling for the new animal drug and includes any event that may be symptomatically and pathophysiologically related to an event listed on the labeling, but differs from the event because of greater severity or specificity. For example, under this definition hepatic necrosis would be unexpected if the labeling referred only to elevated hepatic enzymes or hepatitis.

§ 514.8 [Amended]

10. Section 514.8 *Supplemental new animal drug applications* is amended in paragraph (a)(1) by removing "§ 510.300(a) of this chapter" and by adding in its place "§ 514.80"; in paragraph (a)(5) by removing "§ 510.300(b)(4) of this chapter" and by adding in its place "§ 514.80(b)(4)"; in paragraph (a)(5)(ix) by removing "§ 510.300(b)(1) of this chapter" and by adding in its place "§ 514.80(b)(1)"; and by revising paragraph (a)(6) to read as follows:

(a) * * *

(6) Approval of a supplemental new animal drug application will not be required to provide for an additional distributor to distribute a drug which is the subject of an approved new animal drug application if the conditions described in § 514.80(b)(5)(iii) are met before putting such a change into effect.

* * * * *

§ 514.11 [Amended]

11. Section 514.11 *Confidentiality of data and information in a new animal drug application file* is amended in paragraph (a) by removing "510.300" and adding in its place "514.80".

§ 514.15 [Amended]

12. Section 514.15 *Untrue statements in applications* is amended in paragraph (b) by removing "§ 510.300" and adding in its place "§ 514.80".

13. Section 514.80 is added to subpart B to read as follows:

§ 514.80 Records and reports concerning experience with approved new animal drugs.

The following table outlines the purpose for each paragraph of this section:

Purpose	21 CFR Paragraph and Title
What information must be reported concerning approved NADAs or ANADAs?	514.80(a) Applicability.
What authority does FDA have for requesting records and reports? Who is required to establish, maintain, and report required information relating to experiences with a new animal drug? Is information from foreign sources required?	514.80(a)(1).
What records must be established and maintained and what reports filed with FDA?	514.80(a)(2)
What is FDA's purpose for requiring reports?	514.80(a)(3).
Do applicants of Type A medicated articles have to establish, maintain, and report information required under § 514.80?	514.80(a)(4).
How do the requirements under § 514.80 relate to current good manufacturing practices?	514.80(a)(5).
	514.80(b) Reporting requirements.
What are the requirements for reporting product/manufacturing defects?	514.80(b)(1) Three-day NADA/ANADA field alert report.
	514.80(b)(2) Fifteen-day NADA/ANADA alert report.
What are the requirements for reporting serious and unexpected adverse drug experiences?	514.80(b)(2)(i) Initial report.
What are the requirements for followup reporting of serious and unexpected adverse drug experiences?	514.80(b)(2)(ii) Followup report.
What are the requirements for nonapplicants for reporting adverse drug experiences?	514.80(b)(3) Nonapplicant report.
What are the general requirements for submission of periodic drug experience reports, e.g., forms to be submitted, submission date and frequency, when is it to be submitted, how many copies? How do I petition to change the date of submission or frequency of submissions?	514.80(b)(4) Periodic drug experience report.
What must be submitted in the periodic drug experience reports?	514.80(b)(4)(i) through (b)(4)(iv).
What distribution data must be submitted? How should the distribution data be submitted?	514 80(b)(4)(i) Distribution data.
What labeling materials should be submitted? How do I report changes to the labeling materials since the last report?	514.80(b)(4)(ii) Labeling
	514.80(b)(4)(iii) Nonclinical laboratory studies and clinical data not previously reported.
What are the requirements for submission of nonclinical laboratory studies?	514.80(b)(4)(iii)(A).
What are the requirements for submission of clinical laboratory data?	514 80(b)(4)(iii)(B).
When must results of clinical trials conducted by or for the applicant be reported?	514 80(b)(4)(iii)(C).

Purpose	21 CFR Paragraph and Title
	514.80(b)(4)(iv) Adverse drug experiences.
How do I report product/manufacturing defects and adverse drug experiences not previously reported to FDA?	514.80(b)(4)(iv)(A).
What are the requirements for submitting adverse drug experiences cited in literature?	514.80(b)(4)(iv)(B).
What are the requirements for submitting adverse drug experiences in postapproval studies and clinical trials?	514.80(b)(4)(iv)(C).
What are the requirements for reporting increases in the frequency of serious, expected, and unexpected adverse drug experiences?	514.80(b)(4)(v) Summary report of increased frequency of adverse drug experience.
	514.80(b)(5) Other reporting.
Can FDA request that an applicant submit information at different times than stated specifically in this regulation?	514 80(b)(5)(i) Special drug experience report.
What are the requirements for submission of advertisement and promotional labeling to FDA?	514.80(b)(5)(ii) Advertisements and promotional labeling.
What are the requirements for adding a new distributor to the approved application?	514.80(b)(5)(iii) Distributor's statement
What labels and how many labels need to be submitted for review?	514.80(b)(5)(iii)(A).
What changes are required and allowed to distributor labeling?	514.80(b)(5)(iii)(A)(*1*).
What are the requirements for making other changes to the distributor labeling?	514.80(b)(5)(iii)(A)(*2*).
What information should be included in each new distributor's signed statement?	514 80(b)(5)(iii)(B)(*1*) through (b)(5)(iii)(B)(*5*).
What are the conditions for submitting information that is common to more than one application? (i.e , can I submit common information to one application?)	514.80(c) Multiple applications.
What information has to be submitted to the common application and related application?	514.80(c)(1) through (c)(4).
What forms do I need? What are Forms FDA 1932 and 2301? How can I get them? Can I use computer-generated equivalents?	514 80(d) Reporting forms
How long must I maintain Form FDA 1932 and records and reports of other required information, i.e , how long do I need to maintain this information?	514.80(e) Records to be maintained.
What are the requirements for allowing access to these records and reports, and copying by authorized FDA officer or employee?	514.80(f) Access to records and reports.
How do I obtain Forms FDA 1932 and 2301? Where do I mail FDA's required forms, records, and reports?	514.80(g) Mailing addresses.
What happens if the applicant fails to establish, maintain, or make the required reports? What happens if the applicant refuses to allow FDA access to, and/or copying and/or verify records and reports?	514.80(h) Withdrawal of approval.
Does an adverse drug experience reflect a conclusion that the report or information constitutes an admission that the drug caused an adverse effect?	514.80(i) Disclaimer.

(a) *Applicability.* (1) Each applicant must establish and maintain indexed and complete files containing full records of all information pertinent to safety or effectiveness of a new animal drug that has not been previously submitted as part of the NADA or ANADA. Such records must include information from domestic as well as foreign sources. Each nonapplicant must establish and maintain indexed and complete files containing full records of all information pertinent to safety or effectiveness of a new animal drug that is received or

otherwise obtained by the nonapplicant. Such records must include information from domestic as well as foreign sources.

(2) Each applicant must submit reports of data, studies, and other information concerning experience with new animal drugs to the Food and Drug Administration (FDA) for each approved NADA and ANADA, as required in this section. A nonapplicant must submit data, studies, and other information concerning experience with new animal drugs to the appropriate applicant, as required in this section. The applicant, in turn, must report the nonapplicant's data, studies, and other information to FDA. Applicants and nonapplicants must submit data, studies, and other information described in this section from domestic, as well as foreign sources.

(3) FDA reviews the records and reports required in this section to facilitate a determination under section 512(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360b(e)) as to whether there may be grounds for suspending or withdrawing approval of the NADA or ANADA.

(4) The requirements of this section also apply to any approved Type A medicated article. In addition, the requirements contained in § 514.80(b)(1), (b)(2), (b)(4)(iv), and (b)(4)(v) apply to any approved Type A medicated article incorporated in animal feeds.

(5) The records and reports referred to in this section are in addition to those required by the current good manufacturing practice regulations in parts 211, 225, and 226 of this chapter.

(b) *Reporting requirements*—(1) *Three-day NADA/ANADA field alert report.* This report provides information pertaining to product and manufacturing defects that may result in serious adverse drug events. The applicant (or nonapplicant through the applicant) must submit the report to

the appropriate FDA District Office or local FDA resident post within 3 working days of first becoming aware that a defect may exist. The information initially may be provided by telephone or other telecommunication means, with prompt written followup using Form FDA 1932 "Veterinary Adverse Drug Reaction, Lack of Effectiveness, Product Defect Report." The mailing cover for these reports must be plainly marked "3-Day NADA/ANADA Field Alert Report."

(2) *Fifteen-day NADA/ANADA alert report*—(i) *Initial report.* This report provides information on each serious, unexpected adverse drug event, regardless of the source of the information. The applicant (or nonapplicant through the applicant) must submit the report to FDA within 15 working days of first receiving the information. The report must be submitted on Form FDA 1932, and its mailing cover must be plainly marked "15-Day NADA/ANADA Alert Report."

(ii) *Followup report.* The applicant must promptly investigate all adverse drug events that are the subject of 15-day NADA/ANADA alert reports. If this investigation reveals significant new information, a followup report must be submitted within 15 working days of receiving such information. A followup report must be submitted on Form FDA 1932, and its mailing cover must be plainly marked "15-Day NADA/ANADA Alert Report Followup." The followup report must state the date of the initial report and provide the additional information. If additional information is sought but not obtained within 3 months of the initial report, a followup report is required describing the steps taken and why additional information was not obtained.

(3) *Nonapplicant report.* Nonapplicants must forward reports of adverse drug experiences to the applicant within 3 working days of first receiving the

information. The applicant must then submit the report(s) to FDA as required in this section. The nonapplicant must maintain records of all nonapplicant reports, including the date the nonapplicant received the information concerning adverse drug experiences, the name and address of the applicant, and a copy of the adverse drug experience report including the date such report was submitted to the applicant. If the nonapplicant elects to also report directly to FDA, the nonapplicant should submit the report on Form FDA 1932 within 15 working days of first receiving the information.

(4) *Periodic drug experience report.* This report must be accompanied by a completed Form FDA 2301 "Transmittal of Periodic Reports and Promotional Materials for New Animal Drugs." It must be submitted every 6 months for the first 2 years following approval of an NADA or ANADA and yearly thereafter. Reports required by this section must contain data and information for the full reporting period. The 6-month periodic drug experience reports must be submitted within 30 days following the end of the 6-month reporting period. The yearly periodic drug experience reports must be submitted within 60 days of the anniversary date of the approval of the NADA or ANADA. Any previously submitted information contained in the report must be identified as such. For yearly (annual) periodic drug experience reports, the applicant may petition FDA to change the date of submission or frequency of reporting, and after approval of such petition, file such reports on the new filing date or at the new reporting frequency. Also, FDA may require a report at different times or more frequently. The periodic drug experience report must contain the following:

(i) *Distribution data.* Information about the distribution of each new animal drug product, including information on any distributor-labeled product.

This information must include the total number of distributed units of each size, strength, or potency (e.g., 100,000 bottles of 100 5-milligram tablets; 50,000 10-milliliter vials of 5-percent solution). This information must be presented in two categories: Quantities distributed domestically and quantities exported.

(ii) *Labeling.* Applicant and distributor current package labeling, including package inserts (if any). For large-size package labeling or large shipping cartons, a representative copy must be submitted (e.g., a photocopy of pertinent areas of large feed bags). A summary of any changes in labeling made since the last report (listed by date of implementation) must be included with the labeling or if there have been no changes, a statement of such fact must be included with the labeling.

(iii) Nonclinical laboratory studies and clinical data not previously reported.

(A) Copies of in vitro studies (e.g., mutagenicity) and other nonclinical laboratory studies conducted by or otherwise obtained by the applicant.

(B) Copies of published clinical trials of the new animal drug (or abstracts of them) including clinical trials on safety and effectiveness, clinical trials on new uses, and reports of clinical experience pertinent to safety conducted by or otherwise obtained by the applicant. Review articles, papers, and abstracts in which the drug is used as a research tool, promotional articles, press clippings, and papers that do not contain tabulations or summaries of original data are not required to be reported.

(C) Descriptions of completed clinical trials conducted by or for the applicant must be submitted no later than 1 year after completion of research. Supporting information is not to be reported.

(iv) *Adverse drug experiences.* (A) Product/manufacturing defects and adverse drug experiences not previously reported under § 514.80(b)(1) and (b)(2) must be reported individually on Form FDA 1932.

(B) Reports of adverse drug experiences in the literature must be noted in the periodic drug experience report. A bibliography of pertinent references must be included with the report. Upon FDA's request, the applicant must provide a full text copy of these publications.

(C) Reports of previously not reported adverse drug experiences that occur in postapproval studies must be reported separately from other experiences in the periodic drug experience report and clearly marked or highlighted.

(v) *Summary report of increased frequency of adverse drug experience.* The applicant must periodically review the incidence of reports of adverse drug experiences to determine if there has been an increased frequency of serious (expected and unexpected) adverse drug events. The applicant must evaluate the increased frequency of serious (expected or unexpected) adverse drug events at least as often as reporting of periodic drug experience reports. The applicant must report the increased frequency of serious (expected and unexpected) adverse drug events in the periodic drug experience report. Summaries of reports of increased frequency of adverse drug events must be submitted in narrative form. The summaries must state the time period on which the increased frequency is based, time period comparisons in determining increased frequency, references to any previously submitted Form FDA 1932, the method of analysis, and the interpretation of the results. The summaries must be submitted in a separate section within the periodic drug experience report.

(5) *Other reporting*—(i) *Special drug experience report.* Upon written request, FDA may require that the applicant submit a report required under § 514.80 at different times or more frequently than the timeframes stated in § 514.80.

(ii) *Advertisements and promotional labeling.* The applicant must submit at the time of initial dissemination one set of specimens of mailing pieces and other labeling for prescription and over-the-counter new animal drugs. For prescription new animal drugs, the applicant must also submit one set of specimens of any advertisement at the time of initial publication or broadcast. Mailing pieces and labeling designed to contain product samples must be complete except that product samples may be omitted. Each submission of promotional labeling or advertisements must be accompanied by a completed Form FDA 2301.

(iii) *Distributor's statement.* At the time of initial distribution of a new animal drug product by a distributor, the applicant must submit a special drug experience report accompanied by a completed Form FDA 2301 containing the following:

(A) The distributor's current product labeling.

(*1*) The distributor's labeling must be identical to that in the approved NADA/ANADA except for a different and suitable proprietary name (if used) and the name and address of the distributor. The name and address of the distributor must be preceded by an appropriate qualifying phrase as permitted by the regulations such as "manufactured for" or "distributed by."

(*2*) Other labeling changes must be the subject of a supplemental NADA or ANADA as described under § 514.8.

(B) A signed statement by the distributor stating:

(*1*) The category of the distributor's operations (e.g., wholesale or retail),

(*2*) That the distributor will distribute the new animal drug only under the approved labeling,

(*3*) That the distributor will promote the product only for use under the conditions stated in the approved labeling,

(*4*) That the distributor will adhere to the records and reports requirements of this section, and

(*5*) That the distributor is regularly and lawfully engaged in the distribution or dispensing of prescription products if the product is a prescription new animal drug.

(c) *Multiple applications.* Whenever an applicant is required to submit a periodic drug experience report under the provisions of § 514.80(b)(4) with respect to more than one approved NADA or ANADA for preparations containing the same new animal drug so that the same information is required to be reported for more than one application, the applicant may elect to submit as a part of the report for one such application (the primary application) all the information common to such applications in lieu of reporting separately and repetitively on each. If the applicant elects to do this, the applicant must do the following:

(1) State when a report applies to multiple applications and identify all related applications for which the report is submitted by NADA or ANADA number.

(2) Ensure that the primary application contains a list of the NADA or ANADA numbers of all related applications.

(3) Submit a completed Form FDA 2301 to the primary application and each related application with reference to the primary application by NADA/

ANADA number and submission date for the complete report of the common information.

(4) All other information specific to a particular NADA/ANADA must be included in the report for that particular NADA/ANADA.

(d) *Reporting forms.* Applicant must report adverse drug experiences and product/manufacturing defects on Form FDA 1932, "Veterinary Adverse Drug Reaction, Lack of Effectiveness, Product Defect Report." Periodic drug experience reports and special drug experience reports must be accompanied by a completed Form FDA 2301 "Transmittal of Periodic Reports and Promotional Material for New Animal Drugs," in accordance with directions provided on the forms. Computer-generated equivalents of Form FDA 1932 or Form FDA 2301, approved by FDA before use, may be used. Form FDA 1932 and Form FDA 2301 may be obtained on the Internet at http://www.fda.gov/cvm/forms/forms.html, by telephoning the Division of Surveillance (HFV–210), or by submitting a written request to the following address: Food and Drug Administration, Center for Veterinary Medicine, Division of Surveillance (HFV–210), 7500 Standish Pl., Rockville, MD 20855–2764.

(e) *Records to be maintained.* The applicants and nonapplicants must maintain records and reports of all information required by this section for a period of 5 years after the date of submission.

(f) *Access to records and reports.* The applicant and nonapplicant must, upon request from any authorized FDA officer or employee, at all reasonable times, permit such officer or employee to have access to copy and to verify all such required records and reports.

(g) *Mailing addresses.* Completed 15-day alert reports, periodic drug experience reports, and special drug experience reports must be submitted to

the following address: Food and Drug Administration, Center for Veterinary Medicine, Document Control Unit (HFV–199), 7500 Standish Pl., Rockville, MD 20855–2764. Three-day alert reports must be submitted to the appropriate FDA district office or local FDA resident post. Addresses for district offices and resident posts may be obtained from the Internet at http://www.fda.gov (click on "Contact FDA," then "FDA Field Offices").

(h) *Withdrawal of approval.* If FDA finds that the applicant has failed to establish the required records, or has failed to maintain those records, or failed to make the required reports, or has refused access to an authorized FDA officer or employee to copy or to verify such records or reports, FDA may withdraw approval of the application to which such records or reports relate. If FDA determines that withdrawal of the approval is necessary, the agency shall give the applicant notice and opportunity for hearing, as provided in § 514.200, on the question of whether to withdraw approval of the application.

(i) *Disclaimer.* Any report or information submitted under this section and any release of that report or information by FDA will be without prejudice and does not necessarily reflect a conclusion that the report or information constitutes an admission that the drug caused or contributed to an adverse

event. A person need not admit, and may deny, that the report or information constitutes an admission that a drug caused or contributed to an adverse event.

Dated: March 21, 2003

William K. Hubbard
Associate Commissioner for Policy and Planning

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